REMARKS

In the outstanding Office action, claims 12 to 22 were presented for examination. Claims 12-21 were rejected. Claim 22 was withdrawn from consideration.

In this amendment, applicant has amended claims 12, 15-18 and 21 and has added new claims 23-29 more particularly pointing out the invention. Claims 20 and 22 have been cancelled, without prejudice. Accordingly, claims 12-19, 21 and 23-29 are now pending for examination and, as will be discussed in detail below, it is believed that the application is in condition for allowance.

Specification

The specification has been amended at page 8 to describe an embodiment of gelatine-like protein that can be employed in practicing the claimed invention. Support for this amendment can be found in claim 11 of the original application.

Claim Amendments

Claims 12, 15 to 19 and 21 have amended to delete the respective claim alternative relating to gelatine without narrowing the respective claim alternative relating to a gelatine-like protein.

In addition, claim 12 has been amended to recite that at least 95% of the amino acid residues of the gelatine-like protein consist of Gly-Xaa-Yaa triplets and that the gelatine-like protein comprises at least 15% of proline residues and less than 5% of hydroxyproline residues. Support for the minimum proline and maximum hydroxyproline contents can be found at page 8 lines 12 – 13, and page 8 lines 5 – 6, respectively, of applicant's specification. Support for the limitation as to at least 95% of the gelatine-like protein consisting of Gly-Xaa-Yaa triplets can be found in the paragraph inserted at page 8, line 22 of the specification which inserted paragraph finds support, in its turn, in claim 11 (previously cancelled) as well as in the disclosure at

page 7 lines 10 – 11 of applicant's specification. The substance of the limitations now added to claim 12 could previously be found in now-cancelled claim 20.

Claim 18 has been amended, without narrowing, to recite that the gelatine-like protein has a uniform molecular weight which can optionally be within 2% of a selected molecular weight. Support for this amendment can be found at page 5, lines 1-4 of applicant's specification.

Claims 20 and 22 have been cancelled, without prejudice.

New claim 23 recites that the gelatine-like protein comprises a single polypeptide chain. Support for new claim 23 can be found at page 4, lines 10-11 of applicant's specification.

New claim 24 recites that the gelatine-like protein is essentially free of hydroxyproline residues. Support for new claim 24 can be found at page 6, lines 10-11 of applicant's specification.

New claim 25 recites that the microcarrier beads are formed from a material selected from the group consisting of modified dextran, cross-linked cellulose, porous polystyrene, diethylaminoethyldextran, chemically modified polysaccharides and unmodified polysaccharides and optionally at least 90% of the beads have a size in the range of from 50 µm to 500 µm. Support for new claim 25 can be found at page 6, lines 1-5 and page 9, lines 20-23 of applicant's specification.

New claim 26 recites that the claimed process is employed for producing microcarrier beads coated with the gelatine-like protein in bioreactors, optionally with a loading of microcarrier beads in the bioreactor of from about 20 g/l to 40 g/l. Support for new claim 26 can be found at page 10, lines 19-27 of applicant's specification.

New claim 27 combines limitations appearing in claims 15, 16, 18 and 23.

Claim Objections

In claim 17, the spelling of "immobilizing" has been changed as suggested in the Office action.

Claim Rejections - 35 U.S.C. § 112 First Paragraph

Claims 12-21 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

In reply, applicant respectfully submits that applicant's specification describes the invention as now claimed in amended claim 12 in sufficient detail that a person of ordinary skill in the art will clearly conclude that applicant was in possession of the claimed subject matter at the time the invention was made.

For example, the limitations set forth in amended claim 12 are disclosed in applicant's specification at page 3, lines 25-28 (coating a bead with a gelatine-like protein; the molecular weight range) and in the paragraph inserted at page 8, line 22 of the specification (Gly-Xaa-Yaa triplets, minimum level of proline and maximum level of hydroxyproline).

Directions and guidance regarding the size of gelatine-like protein that is to be employed in the claimed process can be found in applicant's specification at page 4, line 1 to page 5, line 4.

Directions and guidance regarding the content of Gly-Xaa-Yaa triplets and other content of the gelatine-like protein that is to be employed in the claimed process can be found in applicant's specification at page 8, lines 23 to 34.

Directions and guidance regarding the proportion of proline residues that should be present in the gelatine-like protein employed in the claimed process can be found in applicant's specification at page 8, lines 8-21.

Directions and guidance regarding the limited proportion of hydroxyproline residues that can be present in the gelatine-like protein employed in the claimed process can be found in applicant's specification at page 8, lines 1-6.

In reply to the first question on page 3 of the Office action, applicant answers that features that "make the gelatin-like protein similar to a gelatin protein" are described at page 8, line 8 et seq. of applicant's specification. These features can include the absence of non-preferred 3-dimensional globular domains (page 8, lines 9-12). As explained at lines 16-19 of page 8, in designing a suitable protein the skilled person, for instance, with the aid of computer modeling systems, will be able to design sequences comprising proline residues which will not give rise to globular domains. The art discloses the use of computers to assist in discriminating globular and non-globular domains. See, for example, Wootton J.C., Comput. Chem. (1994) 18(3):269-85, "Non-globular domains in protein sequences: automated segmentation using complexity measures", specifically, page 276, 2nd indented paragraph, entitled "4. Segmentation of non-globular regions", which refers to an SEG algorithm which can be employed to partition known domains.

In reply to the second question on page 3 of the Office action, applicant answers that the structure of a gelatine-like protein to be employed in the invention claimed in amended claim 12 which has a molecular weight of 65 kDa as compared with a protein of molecular weight 145 kDa will be shorter with fewer Gly-Xaa-Yaa triplets and fewer prolines and the like.

The structure of gelatine-like protein employable in practicing the process of claim 12 is described in applicant's specification, for example, at page 4, lines 12-19; page 8, lines 1-6 (avoidance of helices); and page 8, lines 8-12.

In addition, an example of a gelatine-like protein that can be employed in practicing the process of amended claim 12 together with the sequence listing of the protein are provided at page 10, line 30 to page 11, line 23 of applicant's specification. Also, methods of production and examples are described in EP 0926543 and EP 1014176 referenced at page 9, lines 1-6 of the specification.

Applicant believes that the above explanation makes it clear that applicant's specification as filed described the invention with sufficient detail for a person of ordinary skill in the art to conclude that applicant was in possession of the invention claimed in amended claim 12.

The dependent claims are also believed to be explicitly and adequately described in the original specification and claims, as is readily apparent or has been explained above.

Claim Rejections - 35 U.S.C. § 102(b) Alleged Anticipation

In the outstanding Office action, claims 12 and 14-18 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Wandrey et al., U.S. Patent No. 5,906,940 ("Wandrey et al."). In addition, claims 12-18 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by International Publication No. WO 91/07485 ("WO 91/07485").

Applicant respectfully believes that neither rejection is relevant to amended claim 12, as will now be explained.

Claim 12, as now amended, relates to a process for the preparation of a cell culture support comprising coating a microcarrier bead with a gelatine-like protein, wherein the gelatine-like protein comprises, inter alia, less than 5% of hydroxyproline residues. Applicant respectfully submits that neither Wandrey et al. nor WO 91/07485 discloses a process wherein microcarrier beads are coated with a gelatine-like protein comprising less than 5% of hydroxyproline residues. Accordingly, applicant believes amended claim 12 is patentably distinguished from each of the references relied upon in the Office action for this reason.

Furthermore, as referenced above, the limitation regarding a low level of hydroxyproline residues, which has been incorporated into amended claim 12, originally appeared in now-cancelled claim 20. Claim 20 was not identified in the Office action as being anticipated by either Wandrey et al. or WO 91/07485. Accordingly, it appears that the Office agrees that the subject matter of amended claim 12, which incorporates the subject matter of now-cancelled claim 20 is distinguished from Wandrey et al. as well as WO 91/07485. Applicant believes this conclusion is implicitly acknowledged in the Office action at page 8, lines 3-4, where reliance is placed upon International Publication No. WO 01/34646 ("WO 01/34646"), and not upon WO 91/07485, for an alleged disclosure of "degree of hydroxylation".

Claim Rejections - 35 U.S.C. § 103 Alleged Unpatentability

In the outstanding Office action, claims 19-21 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over WO 91/07485 in view of WO 01/34646. This rejection is believed to be no more applicable to amended claim 12 than were rejections based on WO 91/07485 alone, as will now be explained.

A benefit obtainable from the invention claimed in amended claim 12 is that of preparing a cell culture support comprising a microcarrier bead coated with a gelatine-like protein which can avoid clumping with other microcarrier beads. This benefit is

obtainable by selecting a gelatine-like coating protein having a relatively narrow molecular weight range and a low hydroxyproline level, pursuant to the requirements of amended claim 12. Two factors contributing to clumping together, or aggregation, of microcarrier beads are believed to be employment of a coating protein which is unduly viscous and employment of a coating protein which is prone to gel.

These problems can be avoided in the practice of the invention claimed in amended claims 12, for reasons which will now be explained. The viscosity of the gelatine-like protein generally is related to its molecular weight. As defined in amended claim 12 the gelatine-like protein has a molecular weight in the range of from about 40 kDa to about 200 kDa. Gelatine-like proteins having a molecular weight in this range generally will have a relatively low viscosity. Accordingly, the claimed molecular weight range should prevent viscosity-related clumping.

Also, as is apparent from page 6, lines 11-12 of applicant's specification, gelation of the gelatine-like protein can be related to the level of hydroxyproline in the protein, as is exemplified by noting that hydroxyproline may form triple helices in collagen (which is described further at page 3, lines 10-12 of applicant's specification). Accordingly, employing a low level of less than 5% of hydroxyproline residues, which is also required by amended claim 12, can avoid gelation of the gelatine-like protein and any resultant clumping together, or agglomeration, of the microcarrier beads.

As alluded to above, a consequence of employing a gelatine-like protein having a low level of hydroxyproline residues is that the gelatine-like protein will not have the helical conformation which natural gelatineusually has. This consequence is believed to be additionally beneficial in avoiding microcarrier agglomeration. Without wishing to be bound by any particular theory, applicant believes that helically conformed gelatine may have less opportunity to adhere to microcarrier bead surfaces, possibly resulting in incomplete covering of microcarrier bead surfaces with gelatine.

Applicant believes that the claimed process of preparing a cell culture support, employing a gelatine-like protein selected to have the molecular weight limits and the low hydroxyproline level defined in amended claim 12, patentably distinguishes the present invention from known microcarrier bead coating processes, whether considered alone or in combination. More particularly, applicant believes the process claimed in amended claim 12 is patentably distinguished from any combination of the disclosures of WO 91/07485 and WO 01/34646.

The Office action alleges that WO 01/34646 discusses the advantages of using "recombinant gelatin, such as . . . specific molecular weight and degree of hydroxylation", citing a number of passages in WO 01/34646. Nevertheless, applicant believes that even when combined with WO 91/07485 these disclosures are not adequate to render the invention of amended claim 12 obvious.

WO 01/34646 describes certain features of recombinant gelatins that are subject to modification. For example, page 28 lines 23 – 33 of WO 01/34646, cited in the Office action, disclose that "recombinant gelatins can be designed to possess the specific characteristics needed for a particular application". However, this is a generalized statement that provides a person of ordinary skill in the art little, if any, guidance as to how to solve the problem of coating microcarrier beads with gelatine without causing clumping. WO 01/34646 is silent as to what specific gelatine characteristics should be modified for which application. Nor does WO 01/34646 describe what parameters should be "finetuned" (WO 01/34646, page 31 line 29) to achieve a particular goal such as preventing clumping of gelatine-coated microcarrier beads.

Furthermore, WO 01/34646 does not appear to identify the disadvantages possessed by conventional gelatins, including conventional recombinantly produced gelatins, when used for coating microcarrier beads, which disadvantages are described

herein. As explained herein, these disadvantages arise because known gelatins contain, or have been designed to contain, naturally found levels of hydroxyproline residues. Still further, the problem of clumping does not appear to be mentioned in WO 01/34646. Since there is apparently no adequate guidance as to which gelatine-like protein parameters should be modified, and solving the problem is not simply a matter of "fine-tuning".

Moreover, the gelatine-like proteins disclosed in WO 01/34646 are described, in Example 2, as being produced by co-expression of prolyl-4-hydroxylase. The resultant gelatine-like proteins accordingly can be expected to contain a substantial amount, for example, more than 10%, of hydroxyproline residues. This conclusion is consistent with the description of known natural gelatine molecules appearing at page 7 lines 28-34 of applicant's specification which estimates approximately 11% hydroxyproline residues are present in a mammalian gelatine. Also, it is noted that the majority of the gelatine-like proteins in Example 2 of WO 01/34646 have a molecular weight that is below the lower molecular weight limit of 40 kDa in amended claim 12. Hence, applicant believes that WO 01/34646 does not suggest applicant's claimed invention to a person of ordinary skill in the art because these practical teachings are contrary to what applicant has claimed.

In summary, the measures provided by the claimed invention to overcome the problem of clumping, notably the employment of a gelatine-like protein having less than 5% hydroxyproline residues and a MW distribution of the gelatine-like protein between 40 kDa and 200 kDa, cannot be determined from WO 01/34646 any more than they can be determined from WO 91/07485. Accordingly, applicant submits that no combination of WO 91/07485 with WO 01/34646 will provide or suggest the invention claimed in amended claim 12. Therefore, applicant believes amended claim 12 is patentable and allowable.

Dependent Claims

Claims 13 to 19, 21 and 23 to 27 depend either directly or indirectly from claim 1, and are therefore believed allowable with claim 1 for the reasons that claim 1 is believed allowable. Dependent claims 13 to 19, 21 and 23 to 27 are furthermore believed clearly and patentably distinguished from the art of record, and therefore allowable, by the additional limitations they recite.

For example, Claims 18 and 27 specifically recites that more than 75% of the gelatine-like protein has a uniform molecular weight. Claim 18 further recites the optional alternative that molecular weight can be within 2% of a selected molecular weight. Applicant submits these limitations are neither disclosed nor suggested by WO 91/07485 or WO 01/34646 or any of the other art of record in this application.

Also, claim 24 specifically recites that the gelatine-like protein is essentially free of hydroxyproline residues which is neither disclosed nor suggested by WO 91/07485 or WO 01/34646 or any of the other art of record in this application.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that consultation with applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to contact the undersigned practitioner.

Respectfully submitted,

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